UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,881	05/15/2006	Hilmar Bischoff		5797

35969 7590 10/18/2006

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
RAHMANI, NILOOFAR	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/531,881	BISCHOFF ET AL.	
	Examiner	Art Unit	
	Niloofar Rahmani	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4-13, 16-18 are pending and claims 2-3, 14-15 are cancelled in the instant application.

2. ***Priority***

This application is filed on 05/15/2006, which is a 371 of PCT/EP03/11619, filed on 10/21/2003, which claims priority of GERMANY 102 50 687.6, filed on 10/31/2002.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-13, 16-18 are rejected because the formulas which represented R^2 is ambiguous. There is no point of attachments in the formulas. Correction is required.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,4-5, 13, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1,4-5, 13, and 16-18 lack description of the claim i.e. " treating or preventing a disorder controlled by inhibition of the cholesterol ester transfer protein (CETP)". Applicant has not shown the nexus for inhibition of the cholesterol ester transfer protein (CETP) and treating or preventing any and all known or unknown diseases. In addition, what diseases are treatable or preventable by inhibition of the cholesterol ester transfer protein (CETP)? Therefore, the specification lacks description of " treating or preventing a disorder controlled by inhibition of the cholesterol ester transfer protein (CETP)".

5. ***Claim Rejections - 35 USC § 112***

Claims 1,4-5, 13, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the

claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 11,page 1 to line 3, page 2 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to medical treatment and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted with disease before the fact. 6) The artisan using Applicants invention would be a Board Certified physician who specialized to treat diseases with an MD degree and several years of experience. Despite intensive

efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of disorder diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent disorder diseases generally. That is, the skill is so low that no compound effective generally against disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula I, I-A, I-B.

The Examiner suggests deletion of the word "prevention".

6. Claims 1,4-5, 13, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because

the specification does not enable the instant compound to alter the gene expression and therefore to treat any and all known or unknown diseases. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to method of treating or preventing a disorder controlled by inhibition of the cholesterol ester protein (CETP), using the compounds of formula I, I-A, I-B.

The state of the prior art: " The development and evaluation of several new therapeutic agents for treatment of blood coagulation disorders are discussed, including glycoprotein (GP) Iib/IIIa antagonists, activators of protease-activated receptors, P2T receptor antagonists, adenosine receptor agonists and serine protease inhibitors. Compounds effective against hypercholesterolaemia, especially inhibitors of cholesterol ester transfer protein (CETP) and acyl coenzyme A:cholesterol acyltrasferse (ACAT) are also addressed. Agents acting via other mechanisms, like the nitric oxide-cGMP (NO-cGMP) pathway, that are involved in cardiovascular effects are discussed."(Lemmens-Gruber et al., Expert Opinion on Therapeutic Patents, 2000, Vol. 10, pages 1354-3776).

" Low density lipoprotein (LDL) was subfractionated by density gradient ultracentrifugation. Postprandial lipoproteins were measured after an oral fat load using retinyl palmitate as a marker for intestinal TG-rich lipoproteins. Hypertriglyceridaemic NIDDMs (HTG) has a preponderance of small dense LDL particles present in the plasma and reduced amounts of large buoyant species when compared to normotriglyceridaemic patients (NTG) and controls. In NIDDM, in the fasting state, the extent of fasting hypertriglyceridaemia, HDL and HL activity are the masjor factors

in predicting the prevalence of small dense LDL particles. Postprandially, the clearance of chylomicron remnants, HL, and insulin resistance are also predictors for the formation of LDL-III in NIDDM." (Tan et al., Atherosclerosis, 1995, Vol. 113, pages 273-287).

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating or preventing diseases against which a regulation of gene expression is efficacious.

Amount of guidance/working examples: However, applicant provides examples of tested compounds and inhibition of the cholesterol ester transfer protein (CETP) in mice, on pages 384-390, Tables I-IV. There is no working example in the instant specification showing that the instant compounds can treat or prevent disorders diseases. Nor are there any examples of the diseases being either treated or prevented by inhibition of the cholesterol ester transfer protein (CETP).

The breadth of the claims: The breadth of claims is drawn to treating or preventing a disorder controlled by inhibition of the cholesterol ester transfer protein (CETP).

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating or preventing diseases against which inhibition of the cholesterol ester protein is efficacious, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 1,4-5, 13, and 16-18, for treating or preventing diseases against which inhibition of the cholesterol ester transfer protein is efficacious, have been enabled by the instant specification.

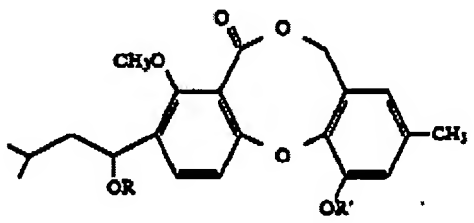
7. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

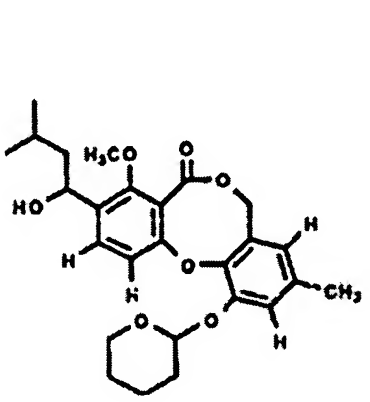
Claims 1,4-5,18 are rejected under 35 U.S.C. 102(b) as being anticipated by Pettibone et al. US 5,198,463. Pettibone et al. disclosed the instant claimed compounds, pharmaceutical compositions, and method of treating a disorder disease using the claimed compounds on column 1, for example



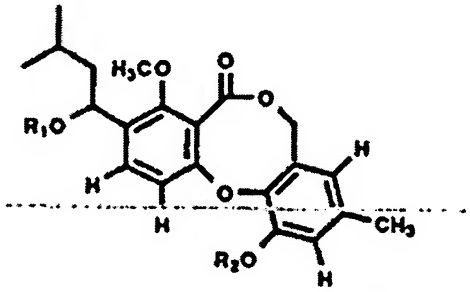
, wherein R being H and R' being CH_3. Therefore, the instant claim is anticipated by Pettibone et al.

8. Claims 1,4-6,11-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Nishida et al. Journal of Antibiotics, 1991, Vol. 44, pages

152-9. Nishida et al. disclosed the instant claimed compounds, pharmaceutical compositions, and method of treating a disorder disease using the claimed compounds on page 153, compounds 4, 9-12, for example



4



9 R_1=H R_2=$CH_3(CH_2)_{14}CO$
10 R_1=R_2=$CH_3(CH_2)_{14}CO$
11 R_1=H R_2=$CH_3(CH_2)_2CO$
12 R_1=R_2=$CH_3(CH_2)_2CO$

, . Therefore, the instant claim is anticipated by Nishida et al.

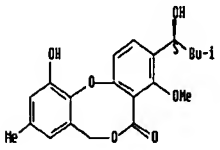
9. Claims 1,4-5, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. Phytochemistry, 1991, Vol. 30, pages 2096-8. Suzuki et al. disclosed the instant claimed compounds, pharmaceutical compositions, and method of treating a disorder disease using the claimed compounds on page 2097, compound #3. Therefore, the instant claim is anticipated by Suzuki et al.

10. Claims 1,4-5, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Frobel et al. US 5,089,487. Frobel et al. disclosed the instant claimed compounds, pharmaceutical compositions, and method of treating a disorder disease using the claimed compounds on columns 31-85, Examples 2-35, 39-63, 68-69, 78-87, 89, 98, 102, 105-106, 109, 11-

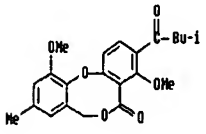
113, 115-116, 119-121, 123-139, 144-145, 149, 152-160, 163-169, 171-187, 192-197, 200,207-208, 212-215, 217-238, 240-258. Therefore, the instant claim is anticipated by Frobel et al.

11. Claims 1,4-5, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Sassa et al., Tetrahedron Letters, 1974, Vol. 45, pages 3941-2. Sassa et al. disclosed the instant claimed compounds, pharmaceutical compositions, and method of treating a disorder disease using the claimed compounds, which are from the STN search

CN 5H,7H-Dibenzo[b,g][1,5]dioxocin-5-one, 11-hydroxy-3-[(1S)-1-hydroxy-3-methylbutyl]-4-methoxy-9-methyl-



CN 5H,7H-Dibenzo[b,g][1,5]dioxocin-5-one, 4,11-dimethoxy-9-methyl-3-(3-methyl-1-oxobutyl)-



. Therefore, the instant claim is anticipated by Sassa et al.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-

272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI
09/25/2006

NR

/MARGARET SEAMAN/
PRIMARY EXAMINER
GROUP 1625